

Environmental Assessment

1. Date: June 19, 1989
2. Name of Applicant: Pfizer Inc.
3. Address: 235 East 42nd Street
New York, New York 10017
4. Description of the Proposed Action:

Pfizer Inc. holds an approved New Animal Drug Application (NADA 113-232) which provides for the safe and effective use of Liqueamycin (oxytetracycline) LA-200 injectable in treating diseases of beef cattle, nonlactating dairy cattle and swine. Oxytetracycline has been used for over 25 years in treating and controlling diseases of food producing animals.

Specifically, the purpose of this proposal is to delete the restriction preventing the use of Liqueamycin LA-200 in treating diseases of lactating dairy cattle. The dosage would be the same as currently approved for the product. Liqueamycin LA-200 is approved for use in cattle for the treatment of pneumonia and shipping fever complex associated with Pasteurella spp. and Hemophilus spp.; foot-rot and diphtheria caused by Fusobacterium necrophorum; bacterial enteritis (scours) caused by Escherichia coli; wooden tongue caused by Actinobacillus lignieresii; leptospirosis caused by Leptospira pomona; and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline. In addition to cattle, oxytetracycline products find widespread use in treating diseases, promoting weight gains and improving feed efficiency in swine, chickens and turkeys, as well as many other species. Due to the widespread use of oxytetracycline, the additional use of this product in lactating dairy cattle will be insignificant and its effect on the environment would be negligible.

The bulk oxytetracycline is manufactured at Pfizer facilities located in Groton, Connecticut; Terre Haute, Indiana or Sandwich, England. The finished product is formulated and packaged at Pfizer's Lee's Summit, Missouri plant. All facilities operate in full compliance with all local, state and federal requirements.

Liqueamycin LA-200 receives the most widespread usage at cattle feedlots. In treating lactating dairy animals usage of the product will occur under pasture conditions as well as in drylots which will be similar to feedlot operations. The primary environment effected by this new usage will be the dairy drylot operation due to the excretion of the drug by treated cattle via their feces and urine and the field fertilized by the excreta from dosed animals. It should be noted that in the treatment of lactating dairy cattle these animals would be treated individually. Rarely, if ever, would more than 5% of a dairy herd be treated at any one particular time.

5. Identification of Chemical Substances:

- a. Trade Name: Terramycin/Liquamycin
- b. Common Name: Oxytetracycline
- c. CAS Registry Number: 79-57-2
- d. Structure and Molecular Weight:

The structure and stereo-chemical configuration of terramycin or 5-oxytetracycline (OTC) has been established by Stephens *et al*, 1950, Waller *et al*, 1952, Schach von Wittenau *et al*, 1956, and Schach von Wittenau and Blackwood, 1960 to be as shown in Figure 1.

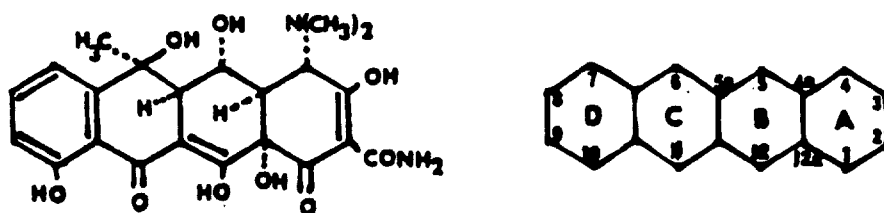


Figure 1. Oxytetracycline

- Melting Point: 184.5°C
- Empirical Formula: C₂₂H₂₄N₂O₉
- Molecular Weight: 498.49
- e. Chemical Name: **Oxytetracycline.** 4-(Dimethylamino)-1,4,4a, 5,5a,-6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

6. Introduction of Substances into the Environment:

a. Introduction through the Manufacturing Process

The bulk oxytetracycline is produced at Pfizer's manufacturing facilities located at Groton, Connecticut; Terre Haute, Indiana or Sandwich, England. The finished product (Liquamycin LA-200) is formulated and packaged at the Pfizer facility in Lee's Summit, Missouri. Oxytetracycline has been produced by Pfizer for over 25 years with no adverse effect on the environment. The additional use of oxytetracycline in lactating dairy cattle is expected to increase the use of oxytetracycline by less than 0.6% compared to that currently produced and sold for use in animals. If one would compare the increased usage to that of all tetracyclines produced and sold for use in animals, the total increase would be infinitesimally small.

In Groton, Connecticut; Terre Haute, Indiana and Sandwich, England the oxytetracycline is manufactured in a general purpose fermentation processing plant equipped to meet current environmental standards for emissions discharged into the atmosphere or effluents discharged into the receiving stream. The liquid effluent from the bulk manufacturing process contains conventional pollutants such as BOD and COD. No toxic pollutants are present. The discharge of liquid effluent from the manufacture of oxytetracycline is in compliance with the National Pollutant Discharge Elimination System (NPDES) permits administered by the States of Connecticut and Indiana. The Sandwich, England facility complies with the following U.K. legislation:

- 1) Site effluent tank discharges
- Control of Pollution Act 1974 (Part 2)
- 2) Gas-scrubber emissions
- Emissions into the Atmospheric Regulations 1983
- 3) Incinerator stack emissions
- Control of Pollution Act 1974 (Part 1)
- 4) Waste solvent disposal
- Control of Pollution (Special Wastes) Regulations 1980

Air emissions from the bulk manufacturing process are scrubbed before discharge into the atmosphere and the quantity of air pollutant is relatively small, consisting primarily of insignificant amounts of hydrocarbons from the organic solvents used in the process. All such air emissions comply fully with the Administrative Regulations for the Abatement of Air Pollution of the Connecticut Department of Environmental Protection as well as the corresponding regulations for the State of Indiana.

There are no toxic pollutants generated as a result of the manufacture of the finished product at the Lee's Summit, Missouri facility. All residual material from the manufacturing process is captured and appropriately disposed of in a waste treatment facility. This process does not emit pollutants as defined by the Air Pollution Control Regulations of the Missouri Air Conservation Commission and all operations are in compliance with these regulations. Occupational exposure to air contaminants during both the bulk manufacturing process as well as the finished product process is limited since most of the operations are contained within a closed system. Where incidents of operator exposure occur during the manufacturing process, appropriate personnel protective equipment is prescribed. Exposures in all operations are controlled within the permissible exposure limits for air contaminants established by the Occupational Safety and Health Administration.

b. Introduction of Substances into the Environment through Use of the Product

Liquamycin LA-200 is approved at two different dosages. The most widely used is as a single intramuscular injection at a dose of 20 mg/kg body weight. The product can also be administered by intravenous or intramuscular injection at a dose of 6.6-11 mg/kg body weight daily. The animals to be treated may be contained in a pasture or a drylot dairy operation.

The increased use of oxytetracycline and, therefore, any increased effect on the environment as a result of treating lactating dairy cattle will be insignificant compared to the amount of oxytetracycline currently being used in food producing animals. The increased production of oxytetracycline as a result of this claim is estimated at 5000 kg per year according to the following calculations:

10,000,000	Total number of dairy cows
5%	Percentage of lactating cows expected to be treated with oxytetracycline
<u>500,000</u>	Total number of lactating cows treated with oxytetracycline

Assume 500 kg animal
x 20 mg oxytetracycline per kg

10,000 mg/500 kg animal

$$\frac{500,000 \times 10,000 \text{ mg}}{1,000,000} = 5000 \text{ kg of oxytetracycline}$$

When this additional 5000 kg of oxytetracycline is compared to the estimated annual production of approximately 900,000 kg, it can be readily determined that any additional impact will be insignificant. When compared to the total tetracycline market which is estimated at between 3-4 million kg a year, the impact is nonexistent.

1. Estimated Concentration of Potentially Bioactive Substances in Excreta of Cattle

The following calculations show the expected concentration of oxytetracycline in the waste produced in a drylot dairy operation. Although animals on pasture will also be treated, the drylot environment would be the worst possible case due to the buildup of excreta and its use as fertilizer. Drug buildup in the environment from excreta of grazing cattle is a more remote possibility since the concentration per acre is considerably less.

Weight of cow	500 kg
Dose of oxytetracycline	x 20 mg/kg
Total dose of oxytetracycline	= 10000 mg
Waste produced per cow per day	45 kg
Total time in drylot/year	365 days
Total waste produced	16425 kg

Concentration of drug in waste:

$$\frac{10,000 \text{ mg dose}}{16,425 \text{ kg waste}} = \frac{0.61 \text{ mg}}{\text{kg}} = 0.61 \text{ ppm}$$

The level of 0.61 ppm would be the average concentration of oxytetracycline assuming all of the administered drug is excreted as biologically active and all animals in the drylot are treated. In reality, only 25% to 75% of the administered dose of oxytetracycline is excreted as biologically active and rarely would greater than 5% of the herd be treated. Therefore, the level of 0.61 ppm would be considerably higher than the level actually expected.

If one considers the first-week's waste and assumes 75% of the total dose is excreted as biologically active compound, then the concentration of drug in the first week's waste would be as calculated below. This again assumes that all cattle are treated where, in reality, only a small number will receive drug treatment.

$$\frac{.75 \times 10,000 \text{ mg}}{7 \text{ days} \times 45 \text{ kg/waste/day}} = 23.8 \text{ ppm}$$

This level of 23.8 ppm would clearly be "the worst case" level of residue in the excreta.

2. Estimated Concentration of Potentially Bioactive Substances Expected in Runoff from Open Air Drylot Operation

Based upon a 20 mg/kg dose for a 500 kg animal in an open air drylot at 110 head/acre (400 sq.ft./cow) the concentration of oxytetracycline drug residue in a 2-inch runoff can be estimated from the following calculation, assuming 1 acre-inch of water equals 102,750 kg.

$$\frac{10000 \text{ mg}}{\text{animal}} \times \frac{110 \text{ animals}}{\text{acre}} \div 205,500 \text{ kg} = 5.4 \text{ mg/kg (ppm)}$$

3. Estimated Concentration of Potentially Bioactive Substances Expected when Excreta of Target Animals are Incorporated into Agricultural Soil as Fertilizer

Using the average estimated concentration of drug residue in drylot wastes of 0.61 mg/kg, an application rate of 4.5×10^3 kg/acre (about 5 tons/acre), and a weight of 909,000 kg soil per acre at 6-inch depth, the concentration of drug residue in the soil would be only .003 ppm.

$$\frac{0.61 \text{ mg oxytet.}}{\text{kg feces}} \times \frac{4.5 \times 10^3 \text{ kg feces}}{\text{acre}} \div \frac{909,000 \text{ kg soil}}{\text{acre}} = .003 \text{ ppm}$$

Using the worst case concentration of drug residue of 23.8 mg/kg and 12 tons per acre (1.09×10^4 kg/acre) which is the highest application rate recommended by USDA, the concentration of drug residue in the top 6 inches of soil from use of the feces from dosed animals as fertilizer would be:

$$\frac{23.8 \text{ mg oxytet.}}{\text{kg waste}} \times \frac{1.09 \times 10^4 \text{ kg waste}}{\text{acre}} \div \frac{909,000 \text{ kg soil}}{\text{acre}} = .29 \text{ ppm}$$

7. Fate of Emitted Substances in the Environment:

The fate of oxytetracycline in the environment has previously been addressed in an Environmental Assessment prepared by the Center for Veterinary Medicine's Environmental Staff. A copy of this report is included which addresses the major environmental transport and transformation processes involved with oxytetracycline. Also included is additional information on the physical/chemical properties, mechanism of action and metabolism of oxytetracycline:

8. Environmental Effects of Released Substances:

The attached Environmental Assessment prepared by CVM thoroughly addresses the environmental effects of oxytetracycline. Based on this information the projected use of oxytetracycline in lactating dairy cattle poses no significant adverse effects on either the terrestrial or aquatic environments and in many instances would be considered beneficial. With regard to plants or animals, it is clear that the use of oxytetracycline at the proposed level is beneficial and does not compromise or pose significant adverse environmental effects on either group.

9. Use of Resources and Energy:

There would be no major commitment of resources with the proposed action. Only the negligible amount of energy and raw materials consumed in the manufacturing process, none of which constitute a significant commitment of resources, would be required.

10. Mitigation Measures:

There are no anticipated adverse environmental impacts associated with the proposed action. All by-products from the manufacturing process are handled in accordance with applicable environmental requirements of various laws.

11. Alternatives to the Proposed Action:

There have been no potential adverse environmental impacts identified for the proposed action, instead this action in certain cases may benefit the environment. The only alternative would be not to approve this requested action which would deny the dairy producer of a highly effective and convenient treatment for various disease conditions afflicting the dairy cow.

The undersigned applicant certifies that the information furnished in this Environmental Assessment is true, accurate and complete to the best of his knowledge.



Signature

Manager, Regulatory Affairs
Title